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COMMENTS ON CITIZEN PETITION
Docket # 2004P-0043

The undersigned submits these Comments on the January 23, 2004 Citizen Petition filed by Richard Blumenthal, Attorney General, State of Connecticut on behalf of Purdue Pharma L.P. ("Purdue"), holder of approved New Drug Application 20-553 for OxyContin® (oxycodone HCl controlled-release) Tablets, 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg ("OxyContin"). For the reasons discussed below, the Petition should be denied.

I. INTRODUCTION

In his Petition, Attorney General Blumenthal ("Petitioner") contends that prescribing OxyContin for administration more frequently than every twelve hours ("q12h") increases the risk of side effects and adverse reactions, as well as opportunities for diversion. Petitioner therefore requests that FDA require Purdue to take a number of steps to warn healthcare practitioners of these increased risks.

As demonstrated in these Comments, Petitioner's concerns are completely unfounded. Petitioner's arguments about expected plasma levels of oxycodone following administration of OxyContin more frequently than q12h are based upon incorrect assumptions about the pharmacokinetics of OxyContin and ignore data Purdue presented to his Office prior to filing of the Citizen Petition. Once available information about the pharmacokinetics of OxyContin is considered, it is clear that expected plasma levels of oxycodone following administration more frequently than q12h would not result in an increased risk of side effects or adverse reactions.

Similarly, there is no experiential basis to conclude that such dosing regimens increase the risk of side effects and adverse reactions. The "data" Petitioner presents to

support his contentions are incomplete, anecdotal, and at odds with accepted scientific reasoning. As demonstrated below, these data clearly do not support the actions proposed in the Petition.

With respect to diversion, Petitioner presents no evidence supporting his belief that prescribing OxyContin more frequently than q12h increases opportunities for diversion, and Purdue knows of no such data. In fact, logic dictates that legitimate and honest pain patients will take, not sell, the entire daily dose prescribed to them to adequately control their pain. On the other hand, criminal diverters posing as legitimate patients, or actual patients who nevertheless seek to divert a portion of their medications, will presumably abuse or sell all or a portion of the medication prescribed to them, and it matters not whether the prescribed total daily dose is divided into two, three, or even more doses, as they will have the same total daily milligram amount of OxyContin available for diversion.

Purdue promotes the use of OxyContin only on a q12h basis, as this is the only approved dosage regimen reflected in the Package Insert. Purdue intends to continue to promote the proven effectiveness of OxyContin in q12h dosing that distinguishes OxyContin from many competitors. However, in the absence of any reason to believe that prescribing OxyContin for administration more frequently than q12h increases the risks to patients, it would be highly inappropriate to foreclose this practice by warning against it in the Package Insert, via a Dear Healthcare Professional letter, or otherwise. For these reasons, the Citizen Petition should be denied.

II. CHANGES TO THE OXYCONTIN PACKAGE INSERT AND OTHER WARNINGS ARE UNWARRANTED AND INAPPROPRIATE

A. There Is No Basis To Conclude That Dosing OxyContin More Frequently Than q12h Increases The Risk Of Undesirable Side Effects Or Adverse Reactions

(1) Dosing OxyContin At Intervals More Frequently Than q12h Does Not Cause Higher Peak Plasma Concentrations Or Greater Fluctuations In Plasma Concentrations Of Oxycodone Than q12h Dosing

Petitioner's assertion that patients who take OxyContin more frequently than every 12 hours are more at risk of experiencing side effects and adverse reactions is based on demonstrably incorrect assumptions about the impact of such dosing on plasma concentrations of oxycodone. As shown below, contrary to Petitioner's assertions, dosing OxyContin more frequently than q12h does not cause higher peak plasma concentrations, greater peak-to-trough fluctuations in plasma concentrations of oxycodone, or more rapid

"accumulation" of oxycodone in plasma. Therefore there is no basis to suspect that such dosing increases the risk of side effects or adverse reactions.

Petitioner seems to raise safety concerns about two practices. First, Petitioner believes that administering OxyContin three times a day, instead of every 12 hours, increases the risk of side effects and adverse reactions due to increased peak plasma concentrations of oxycodone. Second, and of apparently greater concern to Petitioner, is the possibility that physicians will increase a patient's total daily dose of OxyContin by increasing the dosing frequency to q8h or more frequently, rather than by increasing the q12h doses as recommended in the OxyContin Package Insert. Again, Petitioner's concerns appear to stem from alleged elevated peak plasma concentrations of oxycodone resulting from this method of titration, as well as an alleged potential for rapid and/or greater accumulation of oxycodone in plasma.

Purdue has asked Dr. Jürgen Venitz, a well-known expert in the fields of pharmacokinetics and pharmacodynamics, to evaluate Petitioner's contentions. As Dr. Venitz explains in his attached declaration, well-established pharmacokinetic principles dictate that peak plasma concentrations of oxycodone will not increase in the way Petitioner suggests and therefore there is no reason to believe that dosing OxyContin more frequently than q12h increases the risk of any peak-related side effects and adverse reactions. *See* Declaration of Jürgen Venitz, M.D., Ph.D., attached hereto as Exhibit 1, ¶¶ 19-22 (hereinafter "Venitz Decl.").

With respect to Petitioner's first concern, fundamental pharmacokinetic principles establish that, for a fixed total daily dose of OxyContin, peak plasma concentrations of oxycodone will be slightly *lower*, troughs in plasma concentrations of oxycodone will be slightly higher, and overall fluctuation in plasma concentrations will be slightly *less*, if OxyContin is administered every 8 hours than if OxyContin is administered every 12 hours. Venitz Decl. ¶¶ 19-20, 24. Eight hour dosing therefore entails no greater risk of any peak related side effects than with the clinically-proven, safe and effective 12 hour dosing. Venitz Decl. ¶ 22.

With respect to Petitioner's second concern, of course, increasing the total daily dose of OxyContin results in increased peak, trough, and average plasma concentrations of oxycodone. Venitz Decl. ¶ 16. However, if a given increase in total daily dose is accomplished by adding a third dose (q8h dosing), as opposed to increasing the size of the q12h doses, fundamental pharmacokinetic principles dictate that: (a) the resulting increase in peak plasma concentrations of oxycodone will be slightly smaller; (b) the overall fluctuation in plasma concentrations will be slightly less; and (c) average plasma concentrations will increase by the same amount. Venitz Decl. ¶¶ 20-21. Increasing the total daily dose by

adding a third dose, rather than increasing the q12h dose, does not cause more rapid "accumulation" of oxycodone in the plasma. Venitz Decl. ¶ 20.

Purdue has also consulted with Dr. James Barrett, the President of the Center for Pain Control PC in Wyomissing, Pennsylvania. Dr. Barrett's practice involves the treatment of patients with chronic pain, and he has significant experience treating pain patients with opioids. In addition, Dr. Barrett has a Ph.D. in Pharmacology. *See* Declaration of James Philip Barrett, M.D., Ph.D., attached hereto as Exhibit 2, ¶¶ 1-4 (hereinafter "Barrett Decl."). As Dr. Barrett explains in his attached declaration, Petitioner's safety concerns are unjustified because administering a given total daily dose of OxyContin q8h will decrease peak plasma levels of oxycodone, compared to administration of the same daily dose q12h. Similarly, titrating a patient's total daily dose upward by increasing the frequency of dosing, rather than increasing the q12h doses to achieve the same total daily dose, increases peak concentrations less. Barrett Decl. ¶ 6. Moreover, drawing on his clinical experience, Dr. Barrett explains that the difference in peak concentrations resulting from q8h and q12h administration of the same daily dose are relatively small and generally of little clinical significance. Barrett Decl. ¶ 7.

In sum, Petitioner's concern that dosing OxyContin more frequently than q12h will result in higher peak plasma concentrations, greater fluctuations in plasma concentrations of oxycodone, or more rapid accumulation of oxycodone in plasma is based upon unsupported and demonstrably incorrect assumptions about the pharmacokinetics of OxyContin. In fact, such dosing regimens will result in lower peak plasma concentrations and less overall peak-to-trough fluctuation in plasma concentrations. Accordingly, there is no basis to suspect that a physician's decision to prescribe dosing of OxyContin more frequently than q12h increases the risk of any peak related side effects or adverse reactions. Venitz Decl. ¶ 22; *see also* Barrett Decl. ¶¶ 6-9.

(2) Pharmacokinetic Models, Based On Actual Clinical Data, Confirm That Dosing OxyContin At Intervals More Frequently Than q12h Does Not Cause Higher Peak Plasma Concentrations Or Greater Fluctuation In Plasma Concentrations Of Oxycodone Than q12h Dosing

Dr. Venitz' opinions, based on core, well-established pharmacokinetic principles, are confirmed by an OxyContin-specific model developed by Purdue based on actual clinical data. Venitz Decl. ¶¶ 19-20, 24. As explained in the attached declaration of Dr. Stephen C. Harris, Purdue's Senior Medical Director, Clinical Pharmacology and Clinical Pharmacokinetics, using standard, generally accepted pharmacokinetic modeling techniques, Purdue has developed a model that depicts plasma concentrations of oxycodone following administration of OxyContin in different dosing regimens. *See* Declaration of Stephen C.

Harris M.D., attached hereto as Exhibit 3, ¶ 5 (hereinafter "Harris Decl."). In November 2003, Purdue presented simulations generated by this model to Petitioner's office to demonstrate that Petitioner's purported safety concerns were not justified. Harris Decl. ¶ 4.

The accuracy of Purdue's model has been established by comparing oxycodone concentrations predicted by the model to actual drug concentration data from OxyContin subjects whose data were not used to develop the model. Harris Decl. ¶¶ 6-7. As shown in Exhibits A and B to Dr. Harris' Declaration, there is a very close "fit" between predicted values and actual values, establishing that the model is accurate. *See* Harris Decl. ¶ 7. Dr. Venitz has also evaluated Purdue's model and concluded that it accurately predicts plasma concentrations of oxycodone following administration of OxyContin. Venitz Decl. ¶ 23.

Using this model, Purdue has generated a computer simulation showing oxycodone plasma concentrations in two different dosing regimens of OxyContin – q8h and q12h at the same total daily dose (120 mg). Exhibit C to Dr. Harris' Declaration shows these concentrations starting from hour zero in a patient new to OxyContin. This simulation shows that dosing OxyContin at intervals more frequently than q12h does not raise plasma concentrations or cause greater fluctuations in plasma concentrations. Instead, the q8h regimen produces slightly lower peak concentrations and slightly less peak-to-trough fluctuation than with q12h dosing. Harris Decl. ¶ 8.

To further illustrate this point, Purdue has generated another simulation comparing oxycodone plasma concentrations when a total daily dose of 120 mg of OxyContin is administered q2h, q8h, and q12h. Harris Decl. ¶ 9.

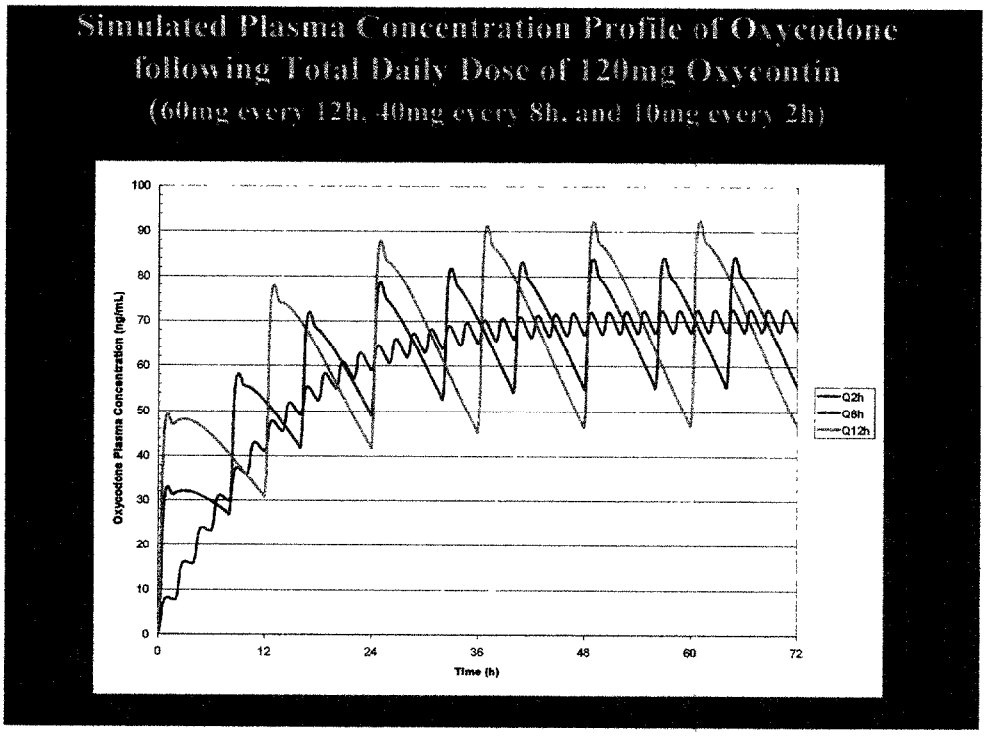
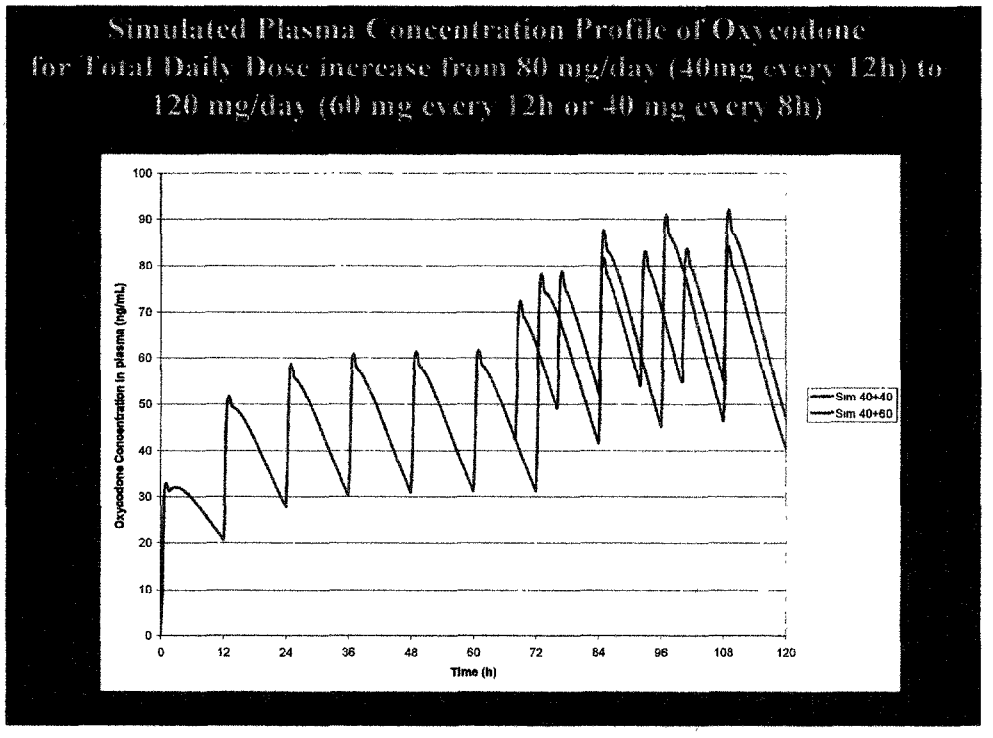


Exhibit D to Dr. Harris' Declaration; *see also* Exhibit E to Dr. Harris' Declaration. This simulation shows that, for a fixed total daily dose, C_{max} (*i.e.*, peak) goes down, C_{min} (*i.e.*, trough) goes up, and overall fluctuation decreases, as the number of divided doses is increased. Harris Decl. ¶ 9.

The same is true if a physician decides to titrate the total daily dose upward by adding a third dose (q8h dosing), rather than by increasing the 12 hour doses. The resulting increase in the total daily dose will typically increase C_{max}; however, the increase in C_{max} will be *smaller* if the increase in total daily dose is accomplished by adding a third daily dose, rather than by increasing the q12h dose. Harris Decl. ¶ 10. Exhibit G to the Declaration of Dr. Harris illustrates this point:



This simulation shows the simulated plasma concentration profile of oxycodone in a patient taking 80 mg/day (40 mg every 12 hours) who is then titrated up to 120 mg/day, either by increasing the 12 hour doses to 60 mg or by adding a third 40 mg dose and changing the dosage frequency to q8h. Again, this simulation shows that increasing the daily dose of OxyContin by adding a third daily dose raises peak plasma concentrations slightly *less* and produces slightly *less* overall fluctuation in plasma concentrations than when the daily dosage is increased by simply raising the q12h doses to achieve that same total daily dose. Harris Decl., ¶ 10.

Similarly, these simulations show that there is no excess or more rapid "accumulation" of oxycodone in plasma with either 12 hour, 8 hour or, indeed, 2 hour dosing at the same total daily dose or when total daily dose is increased by increasing the 12 hour dose or by dividing the increased dose over more frequent doses. In all cases, steady state plasma levels are achieved with OxyContin, as stated in the OxyContin Package Insert, in 24 to 36 hours after first administration or after a dosage adjustment. The average steady-state levels are entirely dependent on the total daily dose and are entirely unaffected by frequency of dosing; while C_{max} at steady-state is slightly lower with more frequent dosing than it is with 12 hour dosing. There is therefore no support whatsoever for the idea that excess or more rapid "accumulation" would result from increasing total daily dosage by increasing the frequency of doses versus increasing the size of the 12 hour doses. Harris Decl. ¶ 11.

In sum, the clinical data and simulations based on those data show that dosing OxyContin more frequently than q12h does not cause higher peak plasma concentrations or greater fluctuations in plasma concentrations of oxycodone or excess or more rapid "accumulation" of oxycodone in plasma, confirming Dr. Venitz' expert opinions and illustrating the fundamental pharmacokinetic principles on which those opinions are based. Venitz Decl. ¶ 24. Accordingly, there is no basis to suspect that such dosing regimens increase the risk of any peak-related side effects or adverse reactions. Harris Decl. ¶ 12; Venitz Decl. ¶ 22.

(3) It Would Be Inappropriate To Warn Against Dosing OxyContin At Intervals More frequently Than q12h

As noted above, Purdue has consulted with Dr. James Barrett, a practitioner with significant experience treating pain patients with opioids. Echoing the opinions of Drs. Venitz and Harris, Dr. Barrett also disagrees with Petitioner's assertion that q8h dosing adversely affects the safety of OxyContin due to alleged higher peak concentrations of oxycodone. Barrett Decl. ¶¶ 6-7, *see supra,* Section II.A.(1). In addition, from a clinical perspective, Dr. Barrett also explains that the other safety concerns mentioned throughout the Petition are likewise unfounded. Barrett Decl. ¶¶ 8-10.

In Dr. Barrett's experience, patients experience pain of varying intensity throughout the day and may experience breakthrough pain at various times for any number of reasons. Accordingly, physicians must tailor both dosage amount and schedule to each individual patient to adequately control pain throughout the patient's typical day, while minimizing side effects. Barrett Decl. ¶ 11. One legitimate technique that may be appropriate for some patients is to prescribe a "q12h" drug like OxyContin on a q8h basis.[1] Dr. Barrett sees no need or justification to warn practitioners against using such techniques to meet the needs of their individual patients. Barrett Decl. ¶ 11.

In short, in the absence of a rational basis for concluding that administration of OxyContin more frequently than q12h increases the risks to patients, it would be inappropriate to foreclose such legitimate medical options that may be appropriate for certain patients by warning against their use. In Dr. Barrett's words:

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[1] Petitioner contends that medical journal articles suggesting administration of OxyContin more frequently than q12h reflect misinformation among the medical community, further underscoring the need for labeling changes warning against this practice. In fact, these journal articles instead support Dr. Barrett's expert opinion that use of OxyContin q8h is a legitimate, recognized technique that can optimize treatment for particular patients without adversely affecting the safety profile of the drug.

> [I]n my view, any requirement for a label statement such as the Petition suggests would not only be scientifically unjustified but would be a serious disservice to the treating physician in restricting dosing options and adjustments which may appropriately be used to better meet the particular needs of their patients.

Barrett Decl. ¶ 12.

(4) Petitioner's Analysis Of MEDWATCH Data And Other Anecdotal Information Proves Nothing

Petitioner's analysis of MEDWATCH data and its other anecdotal information do not establish that prescribing OxyContin for administration q8h or more frequently may increase the potential for side effects and adverse reactions. MEDWATCH is the FDA Medical Products Reporting Program, and the data include adverse experience reports submitted by manufacturers, such as Purdue, and spontaneously by others. Petitioner's MEDWATCH analysis suffers from two fatal flaws. First, the analysis is premised on the erroneous assumption that the adverse experiences described in the reports were caused by OxyContin. Second, submission of MEDWATCH data is so random, uncontrolled, and potentially fraught with bias that no reliable conclusions along the lines suggested by Petitioner can be drawn from the data.

NDA holders are required to adopt and follow formal procedures for the review and documentation of all complaints of any nature received. One aspect of the required review of such complaints is the assessment of whether the reported information should be classified as an "adverse drug experience" and, if so, whether it should be forwarded to FDA. An adverse drug experience is defined as:

> Any adverse event associated with the use of a drug in humans, *whether or not considered drug related,* including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

21 C.F.R. § 314.80(a) (emphasis supplied). Under applicable FDA regulations, therefore, the receipt, investigation, documentation, and potential forwarding of experience reports to the FDA proceeds without regard to the issue of causation, *i.e.,* whether or not there is any

proven (or even plausible) connection between the experience and the company's product.[2] Purely anecdotal in nature, and generated by laypersons and lawyers, as well as doctors, adverse experience reports do not require a causal relationship between the drug and any observed experience. To the contrary, a person making a voluntary report can attribute to the drug anything at all, from warts to whiplash, without corroboration, medical advice, or an expert's opinion.[3] Because of their unreliability, FDA regulations provide that such reports do not constitute an admission that the adverse experiences reported were caused by the drug product, or even that they occurred:

> A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect.

21 C.F.R. § 314.80(k).

In sum, it is impossible to conclude that the reports Petitioner analyzed reflect experiences caused by OxyContin, much less by the interval between doses of OxyContin.

Another weakness in MEDWATCH data is the completely uncontrolled manner in which it is collected. FDA's system is a passive reporting system. Neither healthcare professionals nor patients are required to report adverse drug experiences to FDA or to manufacturers. In addition, the reporting system incorporates a built-in bias, in that FDA has discouraged healthcare professionals from reporting certain categories of experiences, *i.e.*, those which they do not consider "serious" or "unexpected"[4] – yet such experiences are often reported anyway and experiences that may be appropriate to report are not reported.

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[2] Similarly, FDA has advised healthcare professionals that "causality is not a prerequisite for MEDWATCH reporting." *See* The Clinical Impact of Adverse Event Reporting, A MEDWATCH Continuing Education Article (Oct. 1996), p. 2 (available at: http://www.fda.gov/medwatch/articles/med.pdf). Indeed, this is why the FDA regulations use the terminology "adverse experience" instead of "adverse reaction."

[3] Because adverse experience reports do not prove causation, they are generally inadmissible in products liability actions. *See, e.g., Siharath v. Sandoz Pharmaceuticals Corp.*, 131 F.Supp.2d 1347, 1359-63 (N.D. Ga. 2001), *aff'd, Rider v. Sandoz Pharmaceuticals Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002).

[4] *See* The Clinical Impact of Adverse Event Reporting, A MEDWATCH Continuing Education Article (Oct. 1996), p. 2 (available at: http://www.fda.gov/medwatch/articles/med.pdf).

Because of the spontaneous, voluntary nature of adverse experience reports that may be received by a manufacturer or FDA, and the biases created by the FDA reporting criteria, it is impossible to draw meaningful conclusions from any collection of those reports. A myriad of factors can effect the decision of an individual to report an experience to a drug manufacturer or FDA, including potential liability concerns, the uniqueness of the experience, unfamiliarity with a product (or its newness in the marketplace), publicity, promotional activity by competitors, and other factors. As FDA has recognized, MEDWATCH data are subject to a number of potential biases.[5] Indeed, FDA acknowledges that its system is not designed to evaluate the rate, or impact, of known adverse events.[6]

Simply stated, anecdotal, uncontrolled data are not considered reliable. Recognizing the inherent limitations of anecdotal data, FDA forbids the use of experience reports generated under these uncontrolled conditions as a basis for making comparative safety claims about competing drug products. 21 C.F.R. §§ 201.57(g)(4), 202.1(e)(6)(ii). Similarly, FDA's regulations detailing the requirements for clinical investigations of the safety and effectiveness of drugs expressly state that the Agency will not consider "[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation." 21 C.F.R. § 314.126(e).

Petitioner fails to account for even the most likely biases that may well have influenced its analysis of the OxyContin MEDWATCH data. After excluding reports that appeared to relate to individuals who received OxyContin through illicit sources, Petitioner concluded 1,106 reports most likely related to a patient prescribed OxyContin. However, Petitioner only analyzed 795 of these reports because the remaining 311 reports did not mention dosing frequency.[7] Petitioner fails to consider the possibility that dosing frequency was not mentioned in these 311 reports precisely because it mirrored the q12h frequency recommended in the OxyContin Package Insert. Petitioner also fails to consider the possibility that the experiences of patients prescribed OxyContin q8h or more frequently are systematically more likely to be reported (*e.g.*, because q8h dosing is not recommended in

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5 *See* The Clinical Impact of Adverse Event Reporting, A MEDWATCH Continuing Education Article (Oct. 1996), p. 5 (available at: http://www.fda.gov/medwatch/articles/med.pdf).

6 *See* Managing the Risks From Medical Product Use: Creating a Risk Management Framework, Report to the FDA Commissioner from the Task Force on Risk Management, FDA (May 1999), p. 12 (available at http://www.fda.gov/oc/tfrm/riskmanagement.pdf).

7 The lack of dosing information highlights yet another limitation to MEDWATCH data. FDA recognizes that the data received is often of poor quality and does not allow a full understanding of the adverse experience. *See* Managing the Risks From Medical Product Use: Creating a Risk Management Framework, Report to the FDA Commissioner from the Task Force on Risk Management, FDA (May 1999), pp. 63-64 (available at http://www.fda.gov/oc/tfrm/riskmanagement.pdf).

the product label). Because these and other biases may have affected the data, it is impossible to conclude that there is a correlation between q8h prescriptions and adverse experiences.[8]

The LA County Coroner's report and two interviews conducted by Petitioner are equally anecdotal and therefore equally unpersuasive. Moreover, like the MEDWATCH data, proof of causation is totally lacking. The Coroner's report fails to identify a single individual who died as a result of taking OxyContin as prescribed by a physician, whether q12h or more frequently. While the interviews reflect instances in which OxyContin was prescribed for administration more frequently than q12h, there is no indication that this caused the events described.[9]

In the final analysis, Petitioner's anecdotal information in no way establishes that prescribing OxyContin q8h or more frequently increases the potential for side effects and adverse reactions.

(5) Purdue's Emphasis On q12h Dosing Does Not Reflect Any Safety Concerns

Petitioner points to Purdue sales force training materials emphasizing the importance of q12h dosing as evidence that Purdue itself believes that q8h dosing may increase the risk to patients. This is incorrect. As explained above, Purdue firmly believes that dosing OxyContin more frequently than q12h does not cause higher or greater fluctuations in plasma concentrations of oxycodone, and therefore there is no reason to suspect that such a dosing regimen increases the risk of side effects or adverse reactions.

Petitioner misconstrues the significance of Purdue's training materials on q12h. Purdue emphasizes 12 hour dosing because it iwas the only dosing schedule utilized in the studies Purdue submitted to FDA in support of OxyContin approval; because it is the only dosing schedule which FDA allows Purdue to advocate; because q12h dosing confers additional benefits on patients; and because the 12 hour dosing schedule represents a

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[8] Relying on the Ackerman and Bhakta publications, elsewhere in its submission, Petitioner suggests that over 80% of patients may take OxyContin more than two times per day. If this were true, Petitioner's MEDWATCH analysis would support the opposite conclusion: that a much smaller percentage of adverse experiences were reported to MEDWATCH identifying q8h or more frequently dosing than would be expected based on the overall percentage of prescriptions written for administration q8h or more frequently.

[9] In any event, it is not clear that the description of the interviews accurately reflects the facts, in that the experience of Ms. Griffith has been described differently in other forums. *See, e.g.,* Presentation of Chelly Griffith at the National Center on Addiction and Substance Abuse (CASA) at Columbia University Conference, *Feeling No Pain: Substance Abuse, Addiction and Pain Management* (Feb. 27, 2003). Moreover, Ms. Griffith has now sued Purdue.

significant competitive advantage of OxyContin over other products. For these reasons, Purdue has always trained its sales force to promote q12h dosing only.

B. Information In The Package Insert On Elimination Half-Life And Steady State Levels Is Entirely Accurate

Based on Petitioner's meeting with Purdue representatives, Petitioner argues that the information on elimination half-life provided in the OxyContin Package Insert is incorrect. From this, Petitioner hypothesizes that the 24-36 hour range of time in which a patient will reach steady-state described in the Package Insert may also be incorrect, and may be as long as 48-50 hours. Petitioner then concludes that if the time to reach steady state is actually longer than stated in the Package Insert, physicians may make dosage adjustments too soon, resulting in an unnecessarily high dose of OxyContin, to the detriment of patients.[10]

As explained in the attached declaration of Stephen C. Harris, M.D., Petitioner completely misconstrued the parties' discussion regarding half-lives and its significance. The information in the Package Insert regarding the elimination half-life for oxycodone following administration of OxyContin and the time to reach steady-state levels is entirely accurate. Harris Decl., ¶¶ 13-18. Moreover, as stated in the Package Insert, the information on steady state is derived from clinical trials, not from a calculation based on half-life: "Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours." Purdue submitted these pharmacokinetic studies to FDA as part of its NDA for OxyContin. Harris Decl. ¶ 17. Accordingly, the parties' theoretical discussion of elimination half-life provides no basis to question the accuracy of the experimentally-proven 24-36 hour range. In short, Petitioner's speculation that erroneous information in the Package Insert may induce physicians to make dosage adjustments too soon, before a patient has reached steady-state, is baseless.

C. There Is No Evidence That Prescribing OxyContin More Frequently Than q12h Increases The Risk Of Diversion

Petitioner argues that prescribing OxyContin for administration more frequently than q12h may contribute to the illicit supply of OxyContin. According to Petitioner, the "extra" dose provided when OxyContin is prescribed q8h may be an opportunity for diversion in that unscrupulous pain patients may sell the "extra" dose.

Petitioner cites no data or analyses in support of its contention that prescribing OxyContin more frequently than q12h may increase diversion, and Purdue is not aware of

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[10] The Affidavit of James E. O'Brien, Ph.D, M.D., makes these same points in paragraph 8.

any data or other information that would support this theory. In fact, when an honest pain patient with a legitimate medical need for an opioid requires a certain total daily dose of OxyContin for adequate pain relief, it does not matter whether that total daily dose is divided into two or three doses, because the patient will need to use all of that medication to achieve adequate pain relief.[11] In contrast, a criminal diverter posing as a legitimate pain patient (or a pain patient who intends to divert a portion of his medications) will presumably abuse or sell all or a portion of the medication prescribed to him, and it does not matter whether he is prescribed his total daily dose q8h or q12h because he will have the same total milligram amount of OxyContin available for diversion.

D. Petitioner Overstates The Number Of Prescriptions Written For Dosing Intervals Shorter Than q12h

Petitioner claims that a relatively large percentage of OxyContin prescriptions is written for dosing more frequently than q12h, and argues that the trend is increasing. As discussed above, Purdue firmly believes that there is no basis to conclude that this practice increases the risk of side effects or adverse reactions. Accordingly, Purdue does not believe that the extent of this practice is relevant to the Agency's review of the Citizen Petition. Nevertheless, Purdue does note that the practice is less common than Petitioner suggests. Indeed, 2003 IMS data indicate a trend away from prescribing OxyContin for 3/day or more frequent administration.

The Ackerman study cited by Petitioner does not provide reliable data on the percentage of OxyContin prescriptions written for administration more frequently than q12h. As an initial matter, due to its narrow scope, the study is of limited utility in determining the extent to which OxyContin is prescribed for administration more frequently than q12h. The study assessed patient-reported utilization among patients seeking treatment for chronic non-malignant pain at six outpatient pain clinics between August 2001 and January 2002. As the authors acknowledge, actual patient consumption may not reflect prescribing patterns. Moreover, patients with nonmalignant pain referred to outpatient pain clinics are often not representative of the general population of pain patients. Therefore, as the authors concede, the results may not be generalizable to either malignant pain patients or patients who seek medical care in other settings, such as a typical primary care setting.

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[11] Petitioner's hypothesis that patients prescribed OxyContin q8h will necessarily have an "extra" tablet available for diversion because OxyContin controls pain for 12 hours is flawed. While OxyContin does indeed provide 12 hours of pain relief when the correct daily dose is administered in two doses 12 hours apart, if the physician instead divides the correct total daily dose into three doses for q8h administration, the patient will need to take all three doses to obtain the correct total daily dose and achieve adequate pain relief.

Moreover, and of overarching significance, there is no evidence that patients were properly titrated prior to entering the study. The study report describes no specific or uniform methodology, and none of the inclusion criteria suggests that the investigators confirmed that patients were properly titrated. Many patients reported inadequate pain relief, further indicating that patients were not properly titrated to adequate analgesic effect. Therefore, patients may not have received the appropriate dosage to obtain adequate analgesic efficacy, potentially resulting in patients taking OxyContin more frequently than prescribed in an attempt to adequately control their pain. Finally, the questionnaire required patients to identify administration times in two hour blocks. Therefore, patients were unable to specify the actual time they took OxyContin. The authors acknowledged this imprecision as yet another limitation of the study.[12]

In sum, Petitioner overstates the number of prescriptions written for dosing intervals shorter than q12h, and the available data indicate a trend away from prescribing OxyContin for 3/day or more frequent administration.

III. CONCLUSION

As demonstrated in these comments, contrary to Petitioner's contentions, dosing OxyContin at intervals more frequently than q12h does not cause higher or more fluctuating plasma concentrations of oxycodone than q12h dosing. In fact, for a fixed total daily dose, C_{max} goes down slightly, C_{min} goes up slightly, and overall peak-to-trough fluctuation decreases as the number of divided doses is increased. Similarly, titrating the total daily dose upward by adding a third dose, as opposed to increasing the 12 hour dose, results in slightly smaller increases in C_{max} and slightly less fluctuation in plasma concentrations. In no case do these dosing regimens result in excess or more rapid "accumulation" of oxycodone in plasma. Therefore, there is no basis to conclude that such dosing regimens increase the risk of side effects.

Nor has Petitioner shown that there is any data-driven basis to conclude that prescribing OxyContin more frequently than q12h increases the risk of side effects. The anecdotal information submitted by Petitioner is a biased and incomplete collection of incidents from which no reliable conclusions can be drawn.

Finally, Petitioner has provided no support for its speculation that dosing OxyContin more frequently than q12h contributes to diversion.

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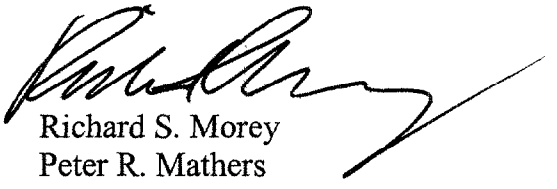
[12] The Adams abstract cited by Petitioner also provides unreliable data. The abstract reports on a small, retrospective chart review of patients from one pain treatment center, not a controlled study. Based on the limited information provided in the abstract, the review suffers from many of the same flaws as the Ackerman study and provides no proper basis on which to draw generalized conclusions.

Because there is no basis to conclude that prescribing OxyContin more frequently than q12h increases the risk of side effects or adverse reactions, or increases opportunities for diversion, and because physicians may properly choose to prescribe the product on different dosage schedules, there is no need to warn against alternate dosing regimens. For this reason, the absence of such warnings does not constitute a "failure to warn" physicians and does not misbrand OxyContin. Indeed, in the absence of a rational basis for concluding that such dosing regimens increase the risks to patients, it would be inappropriate to foreclose such legitimate medical options, that may be appropriate for certain patients, by warning against their use. Therefore, Purdue respectfully urges the Agency to reject the Citizen Petition in its entirety.

Respectfully submitted,



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EXHIBITS

Declaration of Jürgen Venitz, M.D., Ph.D. 1

Declaration of James Philip Barrett, M.D., Ph.D. 2

Declaration of Stephen C. Harris M.D. 3